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Remarks

Receipt is acknowledged of the Office Action of August 7, 2006 in the above-captioned matter. A Request for Continued Examination is included herein. Reconsideration of all of the rejections and a three month extension of the time provided for response are respectfully requested. The Commissioner is hereby authorized to debit all amounts deemed required, including the fees for the RCE, the extension, and the two new claims, from Deposit Account No. 50-1604.

Rejections Under 35 U.S.C. §103

In the Office Action, claims 1-3, 7-8, 17, 19-21, 22, 25-26, 36, and 39-56 were rejected under 35 U.S.C. §103 based on Dellinger (U.S. Patent No. 5,853,993) in combination with Barbera-Guillem (U.S. Patent No. 6,261,779); claims 18, 35, and 37-38 were rejected based on Dellinger and Barbera-Guillem in combination with Weston et al. (WO99/37805); and claims 4-6, 9-16, 23-24, and 27-34 were rejected based on Dellinger and Barbera-Guillem in combination with Van Ness et al. (U.S. Patent No. 6,361,940). Further thereto, remarks regarding the rejections are provided below. Several amendments to the claims have also been made, including amendments for clarity.

The pending independent claims recite a second component having multiple arms, wherein the arms include a sequence complementary to the capture sequence of the RNA reagent. As acknowledged in the Office Action, Dellinger's complementary sequence is only on a single arm. (It should be noted that claims 1 and 19 recite the use of multiple first arms and multiple second arms, while claim 47 recites multiple arms, said arms each comprising a complement). Accordingly,

no 102 rejections are presently pending based on Dellinger.

Nor would the present claims be obvious in view of a combination of Dellinger with the Barbera-Guillem reference. Dellinger teaches the use of linear single-stranded oligonucleotides. *See*, col. 6 line 48 - col 7 line 8. As shown by his signal components, Dellinger was aware of the use of branches, yet his molecules place the dU or dT oligonucleotide (complementary to the RNA) on a single arm. *See e.g.*, Figs. 3 and 5. Counsel submits that Dellinger's choice to use a linear single arm as the RNA complement, despite use of a branched configuration for his other, signal, component, leads away from use of a branched configuration for the RNA complement. Moreover, the consequences of using branched configurations for both components is open to question (as it, for example, might influence the reaction or assay in some unintended manner, whether due to kinetic or other effects).

Furthermore, there is no evidence of record that combining Barbera-Guillem with Dellinger would even work, much less that it would have a reasonable expectation of success.

Dellinger discusses a method using attachment of multiple reporter probes to a homopolymeric region at the 3' or 5' terminus of a nucleic acid analyte. *See*, Dellinger, col. 4 lines 37-40. These homopolymeric regions include a tract of standard purine or pyrimidine bases. Dellinger, col. 2 lines 66-67. One objective is to provide a method wherein reporter probes are designed to contain stable stem and loop structures for attachment of multiple fluorophores. Dellinger, col. 2 lines 22-26. Dellinger further teaches that it is desirable to use his sequences to form triple helixes, with triple helix detection being a means of enhancing detection of a nucleic

acid. Dellinger, col. 6 lines 49 - col 7 line 1.

Barbera-Guillem, on the other hand, discusses a very different type of system, using quantum dots comprised of a core of "CdX", passivated with a shell preferably comprising "YZ". *See,* Barbera-Guillem, col 10 line 18 et seq. and col. 8 lines 33-46. In the course of an assay, multiple steps are used involving the addition of primary dots and secondary dots in alternate layers to form a dendrimer of multiple layers of these quantum dots. Barbera-Guillem, col. 2 line 37 - line 44.

The two methods are significantly different, as are the main reagents and structures utilized. It is respectfully submitted that there is no evidence that the methods would even be compatible, nor grounds for a reasonable expectation that they could be effectively combined.

Nor is there evidence that a modification of Dellinger using the significantly different methods of Barbera-Guillem would result in a technique that could be used to directly assay RNA, as is required by the claims. Due to the stability issues previously encountered in the art when directly working with RNA in these assays, the RNA was traditionally first converted to cDNA, and the assay then conducted using the cDNA sequences. The present invention overcomes those stability issues and uses RNA directly, thereby avoiding the need to first convert it to cDNA.

Particularly in view of those stability issues previously associated with a direct RNA system, no reference has been provided to any language in Barbera-Guillem which would lead one to modify the Dellinger reference and to reasonably expect a stable and effective result. On the contrary, Barbera-Guillem itself admits that quantum dots can themselves sometimes have their own stability problems and disadvantages. *See e.g.,* col 10 line 55 - col 11 line 15.

Accordingly, for this reason as well, it would not at all be obvious to combine Dellinger with Barbera-Guillem, except in hindsight, especially in view of the prior availability of cDNA to conduct assays. One of ordinary skill would not be motivated to move from a stable system (cDNA), to an assay method using RNA (a molecule traditionally associated with instability in these assays), modified using a method disclosing further potential problems in stability (Barbera-Guillem).

In addition to the above, please note that two new claims have been added herein, dependent on claim 47. Claim 57 recites the further use of a ribonuclease inhibitor, and claim 58 recites the use of a dual channel assay. It is submitted that neither of these methods are taught or suggested by Dellinger or Barbera-Guillem either.

With respect to the rejections of claims 18, 35, and 37-38 further in view of Weston, it is noted that Weston teaches the use of "blocking oligonucleotides" to prevent re-annealing of a target strand with its complementary strand. Weston uses those blocking oligonucleotides for a different purpose than pursued by applicants. As explained in the specification, applicants use blocking nucleic acids to prevent binding of excess dendrimer to microarray features containing short segments of poly dA (or other sequences complementary to the capture sequence), so as to prevent non-specific hybridizations. *See,* para. 0049. It can be further desirable to add blocking nucleic acids to the pre-hybridized RNA/dendrimer to prevent exchange of dendrimers from one target RNA to another. Since the present invention does not use "blocking oligonucleotides" to prevent re-annealing of a target strand with its complementary strand, there would be no reason for one of ordinary skill to look to Weston.

Likewise, Weston also does not teach or suggest use of an LNA nucleotide as part of the capture sequence, as recited in amended claims 50 and 55. In short, the cite referenced in Weston does not teach or suggest the use of blocking nucleic acids or LNA as they are used in the present invention.

Accordingly, in view of the above, reconsideration and withdrawal of the §103 rejections is respectfully requested.

Applicant respectfully requests that further action on the double patenting rejections be maintained in abeyance pending arrival at claim language that is otherwise agreed to be allowable. In addition, in the event that the Examiner is considering further rejection of any of the claims, applicant respectfully requests an interview before any additional Office Actions are issued so as to facilitate agreement on allowable subject matter.

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Respectfully submitted,

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